STUDIES ON THE LOCATION OF THE RECEPTOR SITES IN CUTANEOUS AXON REFLEXES*

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Cutaneous axon reflexes are generally believed to involve peripheral stimulation of nerve endings followed by centripetal conduction to the highest points of ramification from which impulses are then conducted centrifugally along all branches of the fibers to the effector sites (1, 2). An alternate possibility, however, is that the highest points of ramification serve directly as receptor sites so that only efferent impulses need be involved. In the early 1940's Coon and Rothman (2) clearly demonstrated in the cat that the autonomic cutaneous axon reflexes, namely sudomotor and pilomotor, could be elicited in freshly excised pieces of skin indicating that the highest points of nerve fiber ramification involved in these reflexes were in the dermis. They further found that if incisions were made through the skin, the spread of the pilomotor response across the incision was inhibited by cuts going through the entire depth of the skin but not by cuts through half its depth.

So far no direct evidence for centripetal impulse conduction in cutaneous axon reflexes has been presented. On the other hand, in the studies reported below we have found that cutaneous axon reflexes could not be elicited by stimuli applied to nerve endings in the epidermis or papillary corium.

EXPERIMENTAL

Test sites on the flexor forearms of seven normal young adult volunteers were stripped to the glistening level by the Wolf-Pinkus (3) cellophane adhesive tape method with the convenient aid of a skin desquamating machine. Such stripping removes the cutaneous water-electrolyte barrier and permits topically applied pharmacologically active salts to enter the epidermis and upper corium as shown by Lorincz (4) and others. Tests for pilomotor, sudomotor, and vasodilator cutaneous axon reflexes were carried out on these prepared sites. These were done by the topical application, as well as by the subsequent intradermal injection in the same sites for each substance tested, of various appropriate dilutions in physiological saline solution of nicotine picrate, acetylcholine hydrochloride, methacholine hydrochloride (Mecholyl), and histamine hydrochloride.

Similar experiments were carried out using methacholine hydrochloride on the flexor forearms of three normal young adults using the denuded floors of blisters produced at the dermal-epidermal junction by the application of liquid nitrogen 24 hours earlier.

In additional experiments in three of the subjects, observations were made on axon reflex vasodilatation elicited by the introduction of 1:100,000 histamine hydrochloride solutions onto stripped skin, and also into normal skin immediately adjacent to stripped sites which had been superficially anesthetized by the prior topical application of one per cent procaine solution.

RESULTS AND COMMENTS

The results of experiments on axon reflex sweating and pilomotion are summarized in Table I. It is evident that in no instance could these axon reflexes be elicited by the topical application onto stripped or denuded skin by equivalent or even much greater concentrations of the test substances which were effective in eliciting these reflexes when injected intradermally into the same sites. These results indicate that no receptor sites for these axon reflexes are present in the epidermis or uppermost corium.

The results of experiments on axon reflex vasodilatation are shown in Table II. It can be seen that solutions of histamine hydrochloride of 1:1,000,000 concentration or less which could elicit axon reflex vasodilatation upon intradermal injection into stripped sites failed to do so when topically applied to such sites. Inasmuch as sensory nerve fiber endings are present in the epidermis and uppermost corium, this point indicates that these endings cannot be the receptors for axon reflex vasodilatation.

Furthermore, superficial anesthesia induced by the topical application of procaine to stripped

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TABLE I

Summary of studies on axon reflex sweating and pilomotion

Test Substance	Concentration	Method of Cutaneous Application	Axon Reflex Sweating and Pilomotion	No. of Trials
Nicotine picrate	1:1,000	Onto stripped site	0	3
	1:10,000	Intradermally into stripped site	+	3
		Onto stripped site	0	7
	1:50,000	Intradermally into stripped site	+	5
		Onto stripped site	0	5
Acetylcholine	1:20	Intradermally into stripped site	+	3
		Onto stripped site	0	3
	1:200	Intradermally into stripped site	+	3
		Onto stripped site	0	3
Methacholine	1:10,000	Intradermally at site of liquid nitrogen induced blister	+	5
		Onto floor of liquid nitrogen induced blister	0	5

TABLE II

Summary of studies on histamine induced axon reflex vasodilatation

Concentration	Method of Cutaneous Application	Response	No. of Trials
1:20,000	Intradermally	Wheal & flare	3
	Onto stripped site	Wheal & flare	3
1:100,000	Intradermally	Wheal & flare	1
	Onto stripped site	Wheal & flare	1
1:1,000,000	Intradermally	Minimal wheal & flare	3
	Onto stripped site	No response	3
	Intradermally under stripped site	Wheal & flare	3
1:2,000,000	Intradermally	Minimal wheal	3
	Onto stripped site	No response	3
1:10,000,000	Intradermally	Minimal wheal	3
	Onto stripped site	No response	3

sites failed to block the elicitation and extension of axon reflex flares about immediately adjacent histamine wheals. These results contrast with the well-known blocking effect of procaine injected intradermally on the spread of histamine induced axon reflex erythema (5). This point additionally supports the view that the receptors for axon reflex vasodilatation are not present in the epidermis or uppermost corium.

DISCUSSION

Rothman and Coon (2) and subsequently others (6) have well summarized the pharmacophysiological evidence which suggests that points of ramification of cutaneous nerve fibrils involved in axon reflexes behave like ganglion cells. It is therefore, not necessary to invoke the hypothesis that centripetal nerve conduction occurs in so-called cutaneous axon reflexes. Our observations provide good evidence for doubting that cutaneous axon reflexes are true reflexes in the sense that they have afferent and efferent limbs. Rather it would appear that the receptor sites involved in the elicitation of so-called cutaneous axon reflexes are the points of axon ramification in the dermis, so that purely centri-

fugal impulses from these points to the end organs are the only neurophysiologic processes that need be invoked to explain the phenomenon.

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